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Walk, Roger A.
From: Gerhard Scherer [Gerhard.Scherer@abf-lab.com]
Sent: Thursday, August 30, 2001 12:49 PM
To: Roger.A.Walk@pmusa.com
Subject: Biomarkers for smoking

Dear Dr. Walk,
the PM Symposium on biomarkers last week in Cologne was, in my view, highly interesting and stimulating. I was mostly impressed by the broad and fundamental scientific approach of your company to determine the effectiveness of risk-reduced products and I hope it will be sucessful.

Coming back to our conversation about the future cooperation between your research group and the ABF, I would like to put two biomarkers in more concrete terms:

1. Biomarker for acrolein exposure: 3-Hydroxypropylmercapturic acie in urine (HPMA):
In 2000 we presented first results with this biomarker at the AACR conference in San Francisco (ppt file of the poster attached). The HPMA excretion turned out to be significantly related to the smoking dose. In the meantime we have improved the method for determining urinary HPMA and obtained the following characteristics of the method:
Principle of method: LC-MS/MS (APCI) after solid phase exctraction of 1 ml urine.
Ion transfer: 222.1 ---> 91.00 m/z
Internal standard (IS): Isopropylmercapturic acid (206.3 ---> 147.0)
Recovery rate: 90 - 105 %
Precision: 5 % (intra-day); 9 % (inter-day)
Limit of detection (LOD): 11 ng/ml; limit of quantification (LOQ): 33 ng/ml
Range of linearity: 6 - 6000 ng/ml
Sample throughput: 100 samples(single measurements)/week (with present ABF capacity).
Potential for further improvement: Usage of a deuterated HPMA standard

2. Biomarker(s) for 1,3-butadiene exposure:
As discussed at the Cologne Symposium, two mercapturic acids and two valine-hemoglobin adducts have been mainly used as biomarkers for 1,3-butadiene exposed workers, except for 1,3-butadiene in exhalate (which has the disadvantage of a very short half-life). Systematic data of smokers' 1,3-butadiene exposure are lacking.

Mercapturic acids: Of the two identified mercapturic acids (1,2-dihydroxy-4-(N-acetylcysteinyl)butane (MI) and 1-hydroxy-2-(N-acetylcysteinyl)-3-butene (MII)), MI turned out to be the better biomarker for 1,3-butadiene exposure. The ABF can offer the development of an analytical method for the determination of MI in urine of smokers and nonsmokers which is supposed to be similar to the described method for HPMA.

Hemoglobin adducts of 1,3-butadiene: In contrast to other alkylvaline hemoglobin adducts (such as methyl-, hydroxyethyl-, cyanoethyl-), the adduct rates formed by 1,3-butadiene are at least 10 - 100 times lower, requiring more sensitive methods. ABF could offer to develop a GC-MS (NCI) method which should be sentive enough to measure 1,3-butadiene adducts in hemoglobin of smokers. A prerequisite would be to have available suitable internal standards (also in deuterated form). The standards need to be synthesized by a contract laboratory.

I would be very glad if I could further discuss these suggestions with you and your colleagues.

I am looking forward to hearing from you,
best regards

[redacted]

aacr00poster.ppt

Gerhard Scherer